REMARKS

Claims 1-30 were pending in this application. Applicants have by this Amendment canceled claims 2, 4, 6, 8 and 12-30, and amended claims 1, 3, 5, 7 and 9. Thus, claims 1, 3, 5, 7, and 9-11 are currently pending in the subject application.

Applicants have canceled claims 2, 4, 6, 8 and 12-30, and have amended claims 1, 3, 5, 7 and 9 solely to expedite the prosecution of the subject application to patent. Applicants, however, do not relinquish their right to claim or otherwise pursue patent coverage for the canceled or deleted subject matter.

Rejection under 35 U.S.C. § 112, first paragraph -written description

On pages 4-6 of the April 11, 2001 Office Action, the Examiner rejected claims 1-11 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner cited *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991), for the statement that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The Examiner then alleged that the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The Examiner noted that applicant's invention is drawn to a

method of treating or preventing hepatitis C virus (HCV) infection in a subject using an effective amount of **an agent** that is capable of inhibiting the attachment of hepatitis C virus onto cells by specifically binding to the hepatitis C virus envelope E2 protein, wherein the agent is a polypeptide, a pseudo enzyme, a peptidomimetic compound, a nucleic acid, an antibody or its variant thereof. The Examiner stated that in analyzing whether the required written description is met for genus claims, it is first determined whether a representative number of species has been described by their complete structure, and the instant specification teaches that a portion of a protein of unknown function that has a sequence of SEQ ID NO: 1, and called E_0 protein in the present application, and its fragment containing the amino acid sequence of residues 1-120 of SEQ ID NO: 1 are capable of interacting with a portion of hepatitis C virus envelope protein E2, as indicated by results derived from the yeast two-hybrid assay. However, the Examiner alleged that the specification fails to disclose any pseudo enzyme or any peptidomimetic compound or any nucleic acid that are capable of interacting with a portion of hepatitis C virus envelope E2 protein onto cells so as to treat or prevent hepatitis C virus in the method as claimed, nNor does the prior art at the effective filing date of the present application provide such teachings. Next, the Examiner stated that it is determined whether a representative number of species has been described by other relevant identifying characteristics, and that apart from the common functional activity of inhibiting the attachment of hepatitis C virus onto cells, the specification fails to disclose any other relevant structural characteristics among polypeptides, among peptidomimetic compounds, among nucleic acid molecules, among antibodies or their variants; and between each of the class of the molecules encompassed by the term "agent". The Examiner alleged that the claimed invention as a whole is not adequately

described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of the Applicant's filing date. The Examiner alleged that possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of the claimed a pseudo enzyme, a peptidomimetic compound or a nucleic acid that are capable of inhibiting the attachment of hepatitis C onto cells, other than the E_0 protein and its fragment containing the amino acid sequence of residues 1-120, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. The Examiner stated that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it, citing *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed.Cir. 1991), and stated that one cannot describe what one has not conceived, citing *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

In response, to expedite prosecution of the subject application, but without relinquishing their right to claim or otherwise pursue patent coverage for the canceled or deleted subject matter, applicants have amended claims 1, 3, 5, 7, and 9 to recite a method of treating or preventing HCV infection by administering the Eo protein. As the Examiner noted, the subject specification does disclose and does contain a written description of the Eo protein and its fragment of 120 residues,

Eo1. Accordingly, the foregoing rejection on written description grounds does not apply to the amended claims, and should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph - enablement

On pages 6-16 of the April 11, 2001 Office Action, the Examiner rejected claims 1-11 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner summarized the factors to be considered in the determination of an enabling disclosure as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims, citing *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed.Cir. 1988)).

The Examiner then stated that the claims are directed to a method of treating or preventing hepatitis C virus (HCV) infection in a subject comprising administering an effective amount of an agent to the subject, wherein the agent is capable of inhibiting the attachment of hepatitis C virus onto cells and thereby to treat or prevent hepatitis C virus infection, and wherein the agent is a polypeptide (preferably E_0 protein or its variant or more preferably SEQ ID NO: 1 or $E_0$1 protein having amino acids 1-120 of SEQ ID NO: 1), a pseudo enzyme, a peptidomimetic compound, a nucleic acid, an antibody or its variant thereof; and the claims are also drawn to the same method wherein the hepatitis C virus envelope E2 protein comprises amino acid sequence of SEQ

ID NO: 2, or comprises 254 amino acids of SEQ ID NO: 2 or comprises amino acid sequence of SEQ ID NO: 3. The Examiner then alleged that the specification teaches by exemplification that using the yeast two hybrid assay, two clones encoding a portion of a protein were selected from a library of human liver Matchmaker cDNA for interacting with a portion of hepatitis C virus E2 lacking its most hydrophobic, carboxyl terminal domain; the sequence of the encoded portion of a protein is referred to as E_0 protein having the amino acid sequence of SEQ ID NO: 1; and furthermore, the specification teaches that the encoded amino acid sequence containing amino acid residues 1-120 of SEQ ID NO: 1 (or $E_0$1 protein) is also capable of binding to the portion of hepatitis C virus E2 as does the E_0 protein, although at a relatively weaker binding affinity (See specification, pages 18-20).

The Examiner then stated that the above evidence has been noted and considered. However, the Examiner alleged that the evidence can not be extrapolated to the instant claimed invention which is drawn to a method of treating or preventing hepatitis C virus infection in a subject using an agent that is capable of inhibiting the attachment of hepatitis C virus onto cells, with the broad claims encompass an agent that includes a polypeptide, a pseudo enzyme, a peptidomimetic compound, a nucleic acid, an antibody or its variant thereof. The Examiner alleged that the instant specification is not enabled for the claimed invention because it fails to provide any guidance regarding the use of any agent, whether it is a polypeptide, a pseudoenzyme, a peptidomimetic compound, a nucleic acid or an antibody or its variant, that is capable of inhibiting the attachment of hepatitis C virus onto cells to treat or prevent hepatitis C virus infection in a subject. The Examiner also alleged that the specification fails to teach or demonstrate a correlation between

the binding interaction of the E_0 and E_01 proteins with a portion of the hepatitis C virus E2 envelope protein observed via the yeast two hybrid assay with any of the therapeutic effects contemplated by the claimed invention which comprise the inhibition of HCV replication, stopping or delaying the progression of liver disease in a subject. The Examiner alleged that since the prior art at the filing date of the present application does not provide such guidance, it is incumbent upon the instant specification to do so. The Examiner alleged that at the filing date of the present application, standard treatments for patients infected with hepatitis C include therapies using recombinant alpha interferon alone or in combination with the nucleoside analogue Ribavirin, whose actions are not mediated via inhibiting the attachment of hepatitis C virus onto cells (Gish, Seminars in liver disease 19 (S1): 35-47, 1999). Moreover, the Examiner alleged that the physiological art is recognized as unpredictable, citing MPEP 2164.03, and as set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the area; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Therefore, the Examiner alleged that with the lack of guidance provided by the instant specification, it would have required undue experimentation without a predictable expectation of success for one skilled in the art to make and use the claimed

invention. The Examiner then proceeded to discuss the specific agents recited in applicants specification, which discussion is not reproduced here. Finally, the Examiner stated that due to the lack of direction or guidance provided by the specification, the state of the art at the effective filing date of the present application, the unpredictability of the physiological and gene therapy arts, and the breadth of the claims, it would have required undue experimentation without a predictable degree of success for one skilled in the art to make and use the instantly claimed invention.

In response, to expedite prosecution of the subject application, but without relinquishing their right to claim or otherwise pursue patent coverage for the canceled or deleted subject matter, applicants have amended claims 1, 3, 5, 7, and 9 to recite a method of treating or preventing HVC by administering the Eo protein.

The experiments in the subject application clearly show that the Eo protein binds with the HCV envelope protein E2. The E2 envelope protein of HCV has been shown to bind to the plasma membranes of cells and this action of E2 mediates entry of the virus into the cells. See, D. Rosa et al., *PNAS* 93:1759-1763, as discussed on page 3, lines 15-19 of the subject specification. Moreover, E2 and E1 envelope proteins form a heteromeric complex, which has also been shown to be necessary for virus binding to the cells and entry into the cells. See, M. Yi et al., *Virology* 231:119-129, as discussed on page 3, lines 19-21 of the subject specification. With the Eo protein bound to the E2 envelope protein, the E2 protein would not be able to bind to the plasma membranes of cells or to form a heteromeric complex with the E1 envelope protein. Accordingly, by binding the E2 envelope protein, the Eo protein is reasonable expected to block HCV

attachment and entry into cells.

As the Examiner recognizes, neither an actual example nor clinical trials are required to support method of treatment claims. See, e.g., *In re Brana*, 51 F3d 1560 (Fed. Cir. 1995), *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985). Even a rigorous correlation is not required. *Id.* All that is required is a reasonable correlation between the data and the claimed use. *Cross*, @ 1050. The disclosed experiments, when taken together with the knowledge available at the filing date of the subject invention, are reasonably correlated with the claimed method.

Accordingly, the foregoing rejection on enablement grounds does not apply to the amended claims, and should be withdrawn.

Prior Art

On page 17 of the April 11, 2001 Office Action, the Examiner stated that claims 1-11 are free of prior art, and that at the time of the instant invention, the prior art did not teach or fairly suggest a method of treating or preventing hepatitis C virus infection in a subject using an effective amount of an agent that is capable of inhibiting the attachment of hepatitis C onto cells by specifically binding to the hepatitis C virus envelope E2 protein as claimed.

Conclusion

In view of the amendments and remarks hereinabove, applicants maintain that none of the cited references, alone or in combination, teach or suggest applicants' claimed invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejections and objection set forth in the April 11, 2001 Office Action and earnestly solicit allowance of pending claims 1, 3, 5, 7, and 9-11.

No fee, other than the enclosed $55.00 one-month extension of time fee, is deemed necessary in connection with the filing of this Response. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Gary J. Gershik 8/13/01

John P. White Date
Reg. No. 28,678
Gary J. Gershik
reg. No. 39,992

Claims with Revision Shown

1. (Amended) A method of treating or preventing hepatitis C virus infection in a subject which comprises administering an effective amount of an ~~agent~~ Eo protein to the subject, wherein the ~~agent~~ Eo protein is capable of inhibiting the attachment of hepatitis C virus onto cells by specifically binding to the hepatitis C virus envelope E2 protein so as to treat or prevent hepatis C virus infection.

~~2. The method of claim 1, wherein the agent is a polypeptide, a pseudo-enzyme, a peptidomimetic compound, a nucleic acid, an antibody or its variant thereof.~~

3. (Amended) The method of claim 1, wherein the hepatitis C virus envelope E2 protein comprises amino acids having an amino acid sequence ~~of Figure 7,~~ shown in SEQ ID NO:2 (Figure 7).

~~4. The method of claim 1, wherein the variant of the hepatitis C virus envelope E2 protein comprises 254 amino acids of SEQ ID NO:2.~~

5. (Amended) The method of claim 1, wherein the ~~variant of the~~ hepatitis C virus envelope E2 protein comprises amino acids having an amino acid sequence ~~of Figure 8,~~ shown in SEQ ID NO:3 (Figure 8).

~~6. The method of claim 1, wherein the agent comprises a Eo protein or its variant.~~

7. (Amended) The method of claim ~~6~~ 1, wherein the Eo protein

comprises amino acids having the amino acid sequence ~~of Figure 2,~~ shown in SEQ ID NO:1 (Figure 2).

~~8. The method of claim 7, wherein the variant of Eo protein comprises 120 amino acids of SEQ ID NO:1.~~

9. (Amended) The method of claim ~~7~~ 1, wherein the ~~variant of~~ Eo protein comprises an Eo1 protein having amino acids 1-120 of SEQ ID NO:1.

10. The method of claim 1, wherein the cells are liver cells.

11. The method of claim 10, wherein the liver cells are human liver cells.